UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/405,050	09/27/99	SHOENFELD Y	ZAP-1CIPCONC

HM22/0606

JANE A MASSARO
FISH & NEAVE
1251 AVENUE OF THE AMERICAS
NEW YORK NY 10020

EXAMINER	
NAVARRO, A	
ART UNIT	**PAPER NUMBER**
1645	9

DATE MAILED: 06/06/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/405,050	Shoenfield et al
Examiner	**Art Unit**
Mark Navarro	1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on _____.

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-11 and 22-29* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-11 and 22-29* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

Applicant's amendment and Declaration filed March 19, 2001 have been received and entered. Claims 12-21 have been canceled, and new claims 22-29 have been inserted, consequently claims 1-11 and 22-29 are pending in the instant application.

Claim Rejections - 35 USC § 112

1. The rejection of Claims 1-11 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is maintained. Additionally this rejection is applied to newly submitted claims 22-29.

Applicant's have filed a Declaration showing the efficacy of IVIG, $F(ab')_2$ and Fc fragments. Applicant's Declaration is sufficient for each of these recited fragments. The sole fragment which remains non-enabled are single chain immunoglobulins. Applicant's specification and Declaration provide no working examples of generating single chain immunoglobulins. Generation of single chain immunoglobulins requires identifying and removing the variable light and variable heavy chains from each individual antibody. Applicant's have not described the sequence of any such region, consequently generation of single chain immunoglobulins from polyclonal antibodies would require excessive experimentation by one of skill in the art. The scope of the claims must bear a reasonable correlation with the scope of enablement. See In re Fischer USPQ 19 24 (CCPA 1970). Adequate written description requires more than a mere

statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016. One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483. As a suggestion, amendment of the claims to no longer recite "single chain immunoglobulins" will be sufficient to overcome this rejection.

Claim Rejections - 35 USC § 102

2. The rejection of claims 1-2, 7-9 under 35 U.S.C. 102(b) as being anticipated by Chapel *et al* is maintained. Additionally this rejection is applied to newly added claims 25-28.

Applicant's are asserting that several elements of Applicant's amended claims are neither expressly nor inherently disclosed. In particular, the cited references (1) do not disclose the use of fragments, (2) do not disclose the use of IVIG in any patients having metastatic cancer, and (3) disclose only particular dosages of IVIG administered intravenously. Therefore, in the absence of affirmative identification of, or a certainty of the "inherent" presence of, these elements in any of the references, the references cannot be used to bar claims that include one or more of those elements. Applicant's arguments have been fully considered but are not found to be fully persuasive.

Applicant's arguments are not found to be fully persuasive in view of the disclosure of Chapel *et al*. First, Applicant's assert that Chapel *et al* do not disclose the use of fragments. While this statement is correct, none of the rejected claims require fragments of IVIG,

consequently this limitation cannot be used to distinguish over the prior art. Second, Applicant's assert that Chapel *et al* does not indicate that there was any metastasis occurring in the patients that received IVIG. The claims are directed to "inhibiting metastasis" if Chapel *et al* did report that metastasis did occur, Applicant's would have a valid point. However, Chapel *et al* not reporting that metastasis occurred only points to the efficacy of the treatment. Applicant's appear to be asserting that they can administer IVIG to a mammal with a lymphoma and inhibit metastasis, while Chapel *et al* administered IVIG to a mammal with lymphoma but was unsuccessful in inhibiting metastasis, simply because he did "not" disclose that metastasis had occurred. In any event, the function of inhibiting metastasis is the result of the administration of IVIG, in view that Chapel *et al* administered IVIG to a mammal with lymphoma, the disclosure of Chapel *et al* is deemed to anticipate the claimed invention. Finally, Applicant's assert that Chapel disclose only particular dosages of IVIG administered intravenously. However, none of these rejected claims recite any dosage in the first place, consequently any differences in dosage are not germane.

Chapel *et al* (Clin. Res. 1988, 36(3) page 407A) disclose of patients with low grade non-Hodgkin's lymphoma receiving intravenous immunoglobulins. (See abstract).

In view that patients with lymphoma received IVIG as claimed, the result of inhibiting metastasis of the lymphoma is deemed to be an inherent result of the administered IVIG, and consequently anticipates the claimed invention.

For reasons of record in Paper Number 6, as well as the above cited reasons this rejection is maintained.

3. The rejection of claims 1-3, 7-10 under 35 U.S.C. 102(b) as being anticipated by Morell *et al* is maintained. Additionally this rejection is applied to newly added claims 25 and 28.

Applicant's are asserting that several elements of Applicant's amended claims are neither expressly nor inherently disclosed. In particular, the cited references (1) do not disclose the use of fragments, (2) do not disclose the use of IVIG in any patients having metastatic cancer, and (3) disclose only particular dosages of IVIG administered intravenously. Therefore, in the absence of affirmative identification of, or a certainty of the "inherent" presence of, these elements in any of the references, the references cannot be used to bar claims that include one or more of those elements. Applicant's arguments have been fully considered but are not found to be fully persuasive.

Applicant's arguments are not found to be fully persuasive in view of the disclosure of Morell *et al*. First, Applicant's assert that Morell *et al* do not disclose the use of fragments. While this statement is correct, none of the rejected claims require fragments of IVIG, consequently this limitation cannot be used to distinguish over the prior art. Second, Applicant's assert that Morell *et al* does not indicate that there was any metastasis occurring in the patients that received IVIG. The claims are directed to "inhibiting metastasis" if Morell *et al* did report that metastasis did occur, Applicant's would have a valid point. However, Morell *et al* not reporting that metastasis occurred only points to the efficacy of the treatment. Applicant's appear

to be asserting that they can administer IVIG to a mammal with a lymphoma and inhibit metastasis, while Morell *et al* administered IVIG to a mammal with lymphoma but was unsuccessful in inhibiting metastasis, simply because he did "not" disclose that metastasis had occurred. In any event, the function of inhibiting metastasis is a result of the administration of IVIG, in view that Morell *et al* administered IVIG to a mammal with lymphoma, the disclosure of Morell *et al* is deemed to anticipate the claimed invention. Finally, Applicant's assert that Morell disclose only particular dosages of IVIG administered intravenously. However, the only required dosage ranger is in claim 3 which recites 2/g/kg/month. Morell *et al* disclose of administering .4g/kg of IVIG daily for five days. (See page S90 and Figure 3). Five days of 0.4g/kg equals a total of 2g/kg for the treatment, the exact dosage amount required by the claims. Consequently this limitation is completely disclosed by Morell *et al*.

Morell *et al* (Pediatr. Infect Dis. J. Vol. 7, No. 5, pp S87-S91, 1988) disclose of 9 patients who were on cytostatic therapy for non-Hodgkin's lymphoma receiving 0.4g/kg of IVIG daily. Morell *et al* further set forth that of administering IVIG for greater than 5 consecutive days. (See page S90 and Figure 3).

In view that patients with lymphoma received IVIG in an amount of 2g/kg/month as claimed, the result of inhibiting metastasis of the lymphoma is deemed to be an inherent result of the administered IVIG, and consequently anticipates the claimed invention.

For reasons of record in Paper Number 6, as well as the above cited reasons this rejection is maintained.

4. The rejection of claims 1-3, 6-9 under 35 U.S.C. 102(b) as being anticipated by Besa *et al* is maintained. Additionally this rejection is applied to newly added claims 25-28.

Applicant's are asserting that several elements of Applicant's amended claims are neither expressly nor inherently disclosed. In particular, the cited references (1) do not disclose the use of fragments, (2) do not disclose the use of IVIG in any patients having metastatic cancer, and (3) disclose only particular dosages of IVIG administered intravenously. Therefore, in the absence of affirmative identification of, or a certainty of the "inherent" presence of, these elements in any of the references, the references cannot be used to bar claims that include one or more of those elements. Applicant's arguments have been fully considered but are not found to be fully persuasive.

Applicant's arguments are not found to be fully persuasive in view of the disclosure of Besa *et al*. First, Applicant's assert that Besa *et al* do not disclose the use of fragments. While this statement is correct, none of the rejected claims require fragments of IVIG, consequently this limitation cannot be used to distinguish over the prior art. Second, Applicant's assert that Besa *et al* does not indicate that there was any metastasis occurring in the patients that received IVIG. The claims are directed to "inhibiting metastasis" if Besa *et al* did report that metastasis did occur, Applicant's would have a valid point. However, Besa *et al* not reporting that metastasis occurred only points to the efficacy of the treatment. Applicant's appear to be asserting that they can administer IVIG to a mammal with a lymphoma and inhibit metastasis, while Besa *et al* administered IVIG to a mammal with lymphoma but was unsuccessful in inhibiting metastasis,

simply because he did "not" disclose that metastasis had occurred. In any event, the function of inhibiting metastasis is a result of the administration of IVIG, in view that Besa *et al* administered IVIG to a mammal with lymphoma, the disclosure of Besa *et al* is deemed to anticipate the claimed invention. Finally, Applicant's assert that Besa disclose only particular dosages of IVIG administered intravenously. However, the only required dosage ranger is in claim 3 which recites 2/g/kg/month. Besa *et al* disclose of administering .4g/kg of IVIG daily for five days. (See abstract). Five days of 0.4g/kg equals a total of 2g/kg for the treatment, the exact dosage amount required by the claims. Consequently this limitation is completely disclosed by Besa *et al.*

Besa *et al* (American Journal of Medicine Apr. 1988, Vol. 84(4), pp 691-698) disclose of patients with Hodgkin's lymphoma and non-Hodgkin's lymphoma treated with intravenous immunoglobulin (0.4g/kg) daily for five doses followed by maintenance therapy every 21 to 28 days if evidence of recurrence was noted. (See abstract).

In view that patients with lymphoma received IVIG in an amount of 2g/kg/month as claimed, the result of inhibiting metastasis of the lymphoma is deemed to be an inherent result of the administered IVIG, and consequently anticipates the claimed invention.

For reasons of record in Paper Number 6, as well as the above cited reasons this rejection is maintained.

Claim Rejections - 35 USC § 103

5. The rejection of claims 1-3, 5-11 under 35 U.S.C. 103(a) as being unpatentable over Morell *et al* or Besa *et al* in view of Cafiero *et al*, Webb *et al* and Way is maintained, additionally this rejection is applied to newly added claims 22, and 25-28.

Applicant's are asserting that none of the cited references teach or suggest that administration of IVIG is useful for inhibiting metastasis of lymphoma or for the treatment of lymphoma. Applicant's further assert that the combination of these references is improper and ineffective, since none of the references even mention the inhibition of metastasis or treatment of lymphoma, to which Applicant's claims are directed.

Applicant's arguments are not found to be persuasive in view of In re Dillon (CAFC) 16 USPQ2d 1897, which sets forth that "Properties must be considered in the overall evaluation of obviousness, and the lack of any disclosure of useful properties for a prior art compound may indicate a lack of motivation to make related compounds, thereby precluding a *prima facie* case, but it is not correct that similarity of structure and a suggestion of *the activity of an applicant's compounds* in the prior art are necessary before a *prima facie* case is established." Consequently the motivation for administering IVIG as taught by Besa *et al*, Morell *et al* and Chapel *et al* to a mammal subcutaneously has been established relying solely on the teachings of the demonstrated success of IVIG administration to a mammal via intravenous administration, as well as the knowledge by those of skill in the art that IVIG was routinely administered subcutaneously as set forth by Webb *et al*. The applicant's newly discovered properties must be considered in

determining whether a prima facie case of unpatenability is made, along with all the other evidence. Neither structure nor properties can be ignored; they are essential to consideration of the invention as a whole. But discovery of a property of a compound is not evidence in determining whether the prior art makes a case of prima facie obviousness.

The teachings of Morell *et al* and Besa *et al* are set forth above.

Morell *et al* and Besa *et al* do not teach of administering IVIG subcutaneously, or of a treatment modality selected from the group consisting of chemotherapy, immunotherapy, radiation therapy and surgery.

Cafiero *et al* (Surgery Vol. 112, No. 1, pp 24-31, 1992) teach of the administration of IVIG to patients before and after the surgical removal of colon tumors, which resulted in a significant decrease in postoperative infection. (See abstract).

Webb *et al* (Lancet Vol. 337, June 29, 1991, pp 1617-1618) teach of infusing intravenous immunoglobulin subcutaneously. (See page 1617).

Way (Current Surgical Diagnosis & Treatment, Ninth Edition, Norwalk, Connecticut, 1991, page 93) set forth that lymphomas are best treated with radiotherapy and combination chemotherapy. (See page 93).

In view that 1) Morell *et al* and Besa *et al* have disclosed administering 2g/kg/month of IVIG to patients with lymphomas, and that 2) Cafiero *et al* set forth that administration of IVIG both before and after removal of tumors resulted in lower postoperative infections, and that 3) Webb *et al* have taught of administering IVIG subcutaneously, and that 4) Way has taught that

lymphomas are best treated with radiotherapy and combination chemotherapy, it would have been *prima facie* obvious to have treated the patients with lymphoma as set forth by Morell *et al* and Besa *et al* with radiotherapy and combination chemotherapy as taught by Way, and to further administer the IVIG subcutaneously as taught by Webb *et al* and to further administer the IVIG after the treatment in view of the teachings of Cafiero *et al*. One would have been motivated to produce such a method in view of the teachings of Way that lymphomas are best treated with radiotherapy and combination chemotherapy, and in view of the teachings of Caifero *et al* which set forth that patients receiving IVIG after surgery had lower postoperative infections.

For reasons of record in Paper Number 6 as well as the above cited reasons this rejection is maintained.

Double Patenting

6. The rejection of claims 1-11 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-18 of U.S. Patent No. 5,965,130 is maintained. Additionally this rejection is applied to newly added claims 22-29.

Applicant's have indicated a willingness to filed a terminal disclaimer to overcome this rejection, however until a terminal disclaimer is filed and made of record, this rejection is maintained for reasons of record in Paper Number 6.

7. The rejection of claims 1-11 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 5,562,902 is maintained. Additionally this rejection is applied to newly added claims 22-29.

Applicant's have indicated a willingness to filed a terminal disclaimer to overcome this rejection, however until a terminal disclaimer is filed and made of record, this rejection is maintained for reasons of record in Paper Number 6.

The following new grounds of rejection are applied to the amended claims:

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claim 29 is rejected under 35 U.S.C. 102(b) as being anticipated by Vitetta *et al.*

The claim is directed to a method for treating lymphoma in a mammal which comprises administering to the mammal a preparation of fragments of IVIG selected from the group consisting of $F(ab')_2$ Fab' Fab, Fc and single chain immunoglobulins.

Vivetta *et al* (Cancer Research Vol. 51, pp 4052-4058, August 1, 1991) disclose of Fab' fragments attached to ricin A chain being administered to patients with refractory B-cell lymphomas. (See abstract).

Applicant's specification defines IVIG as gamma globulin preparations suitable for intravenous use. (Page 4).

In view that Vivetta *et al* disclose of the intravenous administration of Fab' fragments to a mammal with a B-cell lymphoma, the disclosure of Vivetta *et al* is deemed to anticipate the claimed invention.

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark Navarro, whose telephone number is (703) 306-3225. The examiner can be reached on Monday - Thursday from 8:00 AM - 6:00 PM. The examiner can be reached on alternate Fridays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Lynette Smith can be reached at (703) 308-3909.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Group 1645 by facsimile transmission. Papers should by faxed to Group 1645 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the official Gazette 1096 OG 30 (November 15, 1989). The CMI Fax Center number is (703) 308-4242.

Mark Navarro

Primary Examiner

June 4, 2001